

REMARKS

Claims 1-6, 8-14 and 22-27 are pending¹. Claim 28 has been added. The Examiner has asserted new rejections and maintained one previous rejection against these claims that are rebutted in the following order:

- I. Rejections Under 35 U.S.C. § 103(a)
 - A. Claims 1, 3, 5-6, 8-9, 11, 13-14 and 22-27 are allegedly being unpatentable over Ezaki et al., *Int. J. Sys. Bacteriol.* 39:224-229 (1989), in view of Hayward et al., *Mol. Microbiol.* 35:6-14 (2000); as evidenced by DiRisi.
 - B. Claims 2, 4, 10, and 12 are allegedly being unpatentable over Ezaki et al., *Int. J. Sys. Bacteriol.* 39:224-229 (1989), in view of Hayward et al., *Mol. Microbiol.* 35:6-14 (2000); as evidenced by DiRisi, as applied to Claims 1, 3, 5-6, 8-9, 11, 13-14 and 22-27 above, and in further view of United States Patent No. 6,228,575 To Gingeras.
- II. Rejections Under 35 U.S.C. § 112 ¶ 1
 - A. Claims 1-6, 8-14, and 22-27 are allegedly fail to comply with the written description requirement.
 - B. Claims 22-25 allegedly fail to comply with the written description requirement.

¹ The Applicants note that the Office Action summary page inadvertently does not list Claims 1-6 as pending, although Paragraph 1 of the Detailed Action correctly recites Claims 1-6 as pending.

I. The Claims Are Not Obvious

To establish *prima facie* obviousness, one must: i) point to a basis for combining the references, and ii) show that the references when combined teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and MPEP § 2142; Establishing A *Prima Facie* Case Of Obviousness.

The Applicants submit that the Examiner has not made a *prima facie* case of obviousness. First, there is no basis for the combination. Second, even if (improperly) combined, the references do not teach all of the elements claimed.

A. There Is No Basis For The Combination**1. Hayward et al. Is Non-Analogous Art**

The present claims are directed to identifying bacterial species. Hayward is directed to studying gene expression. Applicants therefore submit that it is non-analogous art. The Federal Circuit has outlined a basic definition for non-analogous art:

The determination whether prior art is analogous involves some factual issues concerning whether the reference is within the field of the inventor's endeavor or reasonably pertinent to the particular problem with which the invention was involved.

Finish Engineering Co., Inc. v. Zerpa Industries, Inc., 806 F.2d 1041, 1 USPQ2d 1114, 1116 (Fed. Cir. 1986). Gene expression is not within the field of speciation. Moreover, the problem the present invention is solving relates to the existing disadvantages of using standard DNA hybridization for speciation, namely, “the laborious nature of pairwise cross-hybridizations, . . . , and the fact that it is impossible to establish a central database using these methods.” (see Background of the present specification). These issues are specific to speciation. As such, Hayward is not pertinent.

Because the Hayward reference is non-analogous art, the set of 103 rejections cannot stand – since each of the two (2) obviousness rejections rely on Hayward.

2. Ezaki et al. Teaches Whole Genome Hybridization

Applicants also submit that there is nothing in Ezaki et al. that would motivate one skilled in the art to depart from whole genome hybridization. The Examiner has

pointed to nothing in Ezaki et al. wherein the authors complain about the limitations of the technique or the resulting data. Why would one skilled in the art depart from whole genome hybridization to the use of genomic fragments? The Examiner has pointed to nothing to support such a departure.

3. The Examiner Fails To Support The Combination

Applicants respectfully ask the Examiner: How would the combination work? The Examiner discusses (see Office Action, p. 9) the fact that Hayward et al. uses a technique on genomes that have not yet been sequenced. Even if true, Hayward et al. uses fragments from a *single* genome. Hayward et al. does not make arrays of multiple genomes, let alone teach a method of sorting out the potentially overwhelming confusion when multiple genomes are arrayed with random sequences. In order to support the combination, the Examiner must demonstrate that the combination would work. Under the law:

There can be no technological motivation for engaging in a modification or combination of references if the modification destroys the intended purpose or function of the invention disclosed in the reference. To the contrary, there would be a disincentive.

In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). The Examiner has not shown that either reference teaches how speciation can be achieved – or that some other knowledge in the art would permit the combination to work.

To underscore this argument, Claims 1 and 9 are further amended to clarify that the genomic sequences are “at least four bacterial reference species”. Other amendments are made to remove unnecessary and/or redundant language. Claims 22-27 were amended to maintain proper antecedent basis. These amendments are made not to acquiesce to the Examiner’s argument but only to further the Applicants’ business interests, better define one embodiment and expedite the prosecution of this application.

B. Even If Combined, All Claim Elements Are Not Taught

Applicants insist the combination is improper in the first place (see above). Without waiving this argument, Applicants submit that even if (improperly) combined, all the elements of the claims are not taught.

1. Ezaki et al. And Hayward et al. Fail To Teach The Use Of Random Genomic Sequences

In regards to Ezaki et al, the Examiner admits that Ezaki et al. fails to teach the use of random genomic sequences:

“Ezaki et al. does not teach providing amplified random genomic sequences ...”

Office Action, pg. 7. The Examiner, however argues that Hayward et al. provide this element. This is incorrect. Hayward’s fragmentation is NOT random. Hayward makes it clear that a technique has been selected to favor fragments containing coding sequences (after all, as pointed out above, Hayward is interested in gene expression):

“Mung bean nuclease preferentially cuts malarial DNA in regions flanking coding regions . . . Such digestion was expected to capture long stretches of unique coding regions and avoid over-representation of flanking sequences or introns on the array.”

(see Hayward et al., p. 7, Array construction). Indeed, Applicants submit that this amounts to a teaching away from the use of random fragments.

2. Ezaki et al. And Hayward et al. Fail To Teach The Use Of A Mere Fraction Of The Genome

As noted above, Ezaki et al. employs whole genome hybridization. Hayward et al. also teach the use of as many genes as possible so that a complete representation is attempted:

“To provide as complete a representation of genes as possible . . . a mung bean nuclease genomic library was used.”

(see Hayward et al, p.7, Array construction). By contrast, the present specification teaches that the technique, in one embodiment, uses a sample that represents between 1 and 3% of the genome:

“Considering that the average genome size of fluorescent Pseudomonas strains is approximately 5 Mb and that the size of the genome fragments used was 1 to 2 Kb, the array used in these Examples sampled approximately 1 to 3% of a genome.”

(See specification, para 0024). To underscore this embodiment, Claim 9 has been amended to introduce this feature.² It should be noted that the use of but a small sample of a genome for speciation is counterintuitive, therefore success (as shown in the present specification) in speciation is surprising.

3. Ezaki et al. and Hayward et al. Fail To Teach A Labeled Target DNA And A Labeled Reference DNA

The Examiner admits that Ezaki fails to “teach labeled target DNA with a first fluorescent dye and labeled reference DNA from a second fluorescent dye.” (Office Action, pgs. 7-8). Indeed, Ezaki et al. is limited to measuring a single fluorescent probe (e.g., 4-methylumbelliferyl-beta-D-galactopyranoside). Nonetheless, the Examiner attempts to remedy this deficiency with Hayward. The Examiner states that:

Hayward et al. teach labeling two different forms of Plasmodium with two different fluorescent labels to evaluate the differences among the two forms ...

Office Action, pg. 8. The Applicant’s submit that Hayward et al. uses two labeled cDNAs both of known origin:

The usefulness of the shotgun microarray for analyzing malarial transcription programmes was evaluated by comparing gene expression between two differentiated forms of Plasmodium. Trophozoite-specific RNA was used as a template to generate Cy3-labelled cDNA (green fluorescence) and late-stage gametocyte-specific RNA was used to generate Cy5-labelled cDNA (red fluorescence).

Hayward et al., pg 7, rhc [emphasis added]. Clearly, in the context of the Applicant’s claimed embodiment, Hayward et al. teaches two labeled reference DNAs. In other words, Hayward et al. does not use either of the two labeled cDNAs to determine its origin (i.e., for example, speciation). This is in stark contrast to the Applicants’ claimed embodiment comprising a first labeled target DNA (e.g., DNA requiring speciation) and a second labeled reference DNA (e.g., DNA whose species is known) that results in the

² The amendment is made to further the prosecution, and clarify one embodiment. Applicants hereby expressly reserve the right to prosecute the unamended claim (or similar claim) in the future.

speciation of the first labeled target DNA. As such, the combination of Ezaki et al. and Hayward et al. do not teach all the elements of the Applicants claimed embodiments by failing to teach a “target DNA” and a “reference DNA”.

4. DeRisi et al. Fails To Teach Determining An Evenness Value

The Examiner combines the cited art with the DeRisi et al. reference as allegedly evidencing that measuring signal intensity ratios is an inherent property of the method of Hayward et al.:

DeRisi et al. reference discloses that processing and recording of signals comprises calculation of a hybridization signal intensity ratio and normalization of the signal ... accordingly it is an inherent property of the method of Hayward to include such a step.

Office Action, pg 7. The Applicants disagree. Moreover, in preferred embodiments, statistical analysis can involve mathematical operations beyond the mere calculation of a ratio. For example, in one embodiment, the Applicants teach the use of an evenness value (i.e., for example, θ_E) that “ranges between 50° - 20°:

To conveniently find conserved and unique (variable) sequences in the fragment collection described in the Examples, an evenness index (E) (Legendre and Legendre, Numerical Ecology, Elsevier Science, Amsterdam [1998]; Pielou, J. Theor. Biol., 13:131-144 [1966]) was calculated from hybridization signal ratio profiles of each spotted genome fragment across the test strains. These results are shown in Figure 5. For fragments that are extremely conserved in all test strains (e.g., rRNA genes), the angle (θ_E) shows its minimum value (0°).

Applicants' Specification, pg. 8 ln 22-28 [emphasis added], and

When the empirical results obtained in the Examples described herein (i.e., θ_E values) were applied to this diagram, the degree of conservation within strain level, species level, closely related species level, and genus level roughly corresponded to θ_E values of > 50°, 50° to 20°, 20° to 10°, and < 10°, respectively. Additionally, a taxonomic distance ($D_{1/\tan(\theta)}$) was calculated ($D_{1/\tan(\theta)} = 1/[\tan(\theta_E)]$). The range of θ_E values for species level (> 20°) in the

experiments described in the Examples resulted in a $D_{1/\tan(\theta)}$ of 2.74, indicating a radius of taxonomic range for a species.

Applicants' Specification, pg. 10 ln 2-9 [emphasis added]. Applicants note the advantages of the evenness value over other approaches. For example, Applicants teach that the technique of cluster analysis does not provide the same resolution as an evenness value:

It is noteworthy that the variable and conserved sequences cannot be reliably identified by cluster analysis (*See, Figure 4*), but are easily revealed by θ_E values.

Applicants' Specification, pg. 9 ln 23-25. To underscore this embodiment, Applicants provide new Claim 28. The new claim is presented without acquiescing to the Examiner's argument but to further the prosecution.

5. Gingeras et al. Teach Known Sequences

The Examiner forms a second obviousness rejection by adding Gingeras et al. to the primary combination of Ezaki et al. and Hayward et al. in view of DeRisi et al. The Applicants submit that because Ezaki et al. and Hayward et al. in view of DeRisi et al. fail to create a *prima facie* case of obviousness, the addition of Gingeras et al. is not helpful. The methods of Gingeras et al. require knowledge of the sequence of the arrayed reference probe and are inoperable without this knowledge. Indeed, the Examiner recognized that “Gingeras teach using known sequences”. *Office Action, page 8, item 12.* Moreover, Gingeras et al. explicitly teaches that:

The methods of this invention employ oligonucleotide arrays which comprise probes exhibiting complementarity to one or more selected reference sequences whose sequence is known.

Gingeras et al., column 13, lines 34-37. This statement, as well as many others detailed in the previous response, unambiguously shows that Gingeras et al. must use arrayed oligonucleotides having a known sequence. Accordingly, Gingeras et al. teaches a strong disincentive to practicing the claimed methods. This, alone, rebuts a *prima facie* case of obviousness, if one were arguably made in the first place.

C. Conclusion

The Applicants have demonstrated above the combination(s) of Ezaki et al., Hayward et al., DeRisi et al., and/or Gingeras et al. fail to create a *prima facie* case of obviousness. In particular, the claimed element of an unknown labeled test DNA sequence that hybridizes to one of at least four reference genomic DNA sequences are not found within these references. That, in itself, is sufficient to rebut a *prima facie* case of obviousness. The Examiner is respectfully requested to withdraw the two obviousness rejections.

II. The Claims Comply With 35 U.S.C. § 112 ¶ 1

A. Claims 1-6, 8-14, and 22-27 Comply With The Written Description Requirement.

The Examiner states that the previous claim amendment:

... identifying without the need for sequencing said amplified genomic sequences is not supported in the specification and raises the issue of new matter.

Office Action, pg. 3. The Applicants disagree and believe that this rejection is now moot due to the above claim amendments made for other reasons. The Examiner is respectfully requested to withdraw the rejection.

B. Claims 22-25 Comply With The Written Description Requirement.

The Examiner states that the previous claim amendment:

... of “at least 60 arrayed elements” and “at least 90 arrayed elements” ... are not supported in the specification and raises the issue of new matter.

Office Action, pg. 4. The Applicants disagree and believe that one having ordinary skill in the art would know that arrays comprising between 60 – 90 elements can be

successfully scaled to larger sizes. In fact, the Examiner admits that this concept is taught:

The Examiner agrees that the specification provides support for ... 60 ... to 500,000 probes.

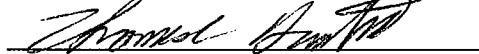
Office Action, pg. 5. The Applicants believe that one having ordinary skill in the art would interpret such a disclosed range supports the Applicant's "at least" claim language. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 22 and 24 to recite "between 60 – 500,000 genomic sequences". Claims 23 and 25 are amended to delete the "at least" limitation. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Examiner is respectfully requested to withdraw the present rejection.

CONCLUSION

In view of the above, Applicants respectfully request withdrawal of the rejections and passing the application to allowance.

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